

CONCISE REPORT

Gluten sensitivity masquerading as systemic lupus erythematosus

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Case reports: Three patients are described whose original presentation and immunological profile led to the erroneous diagnosis of systemic lupus erythematosus. The correct diagnosis of gluten sensitivity was made after years of treatment with steroids and other immunosuppressive drugs.

Conclusions: The immunological profile of IgA deficiency and/or raised double stranded DNA in the absence of antinuclear factor together with raised inflammatory markers and symptoms suggestive of an immune diathesis should alert the physician to the possibility of gluten sensitivity. The presence of an enteropathy is no longer a prerequisite for the diagnosis of gluten sensitivity, which can solely present with extraintestinal symptoms and signs. Knowledge of the diverse manifestations of gluten sensitivity is essential in avoiding such misdiagnosis.

Gluten sensitivity is a state of heightened immunological responsiveness to ingested gluten in genetically susceptible people.¹ It represents a spectrum of diverse manifestations, of which gluten sensitive enteropathy (also known as coeliac disease (CD)) is one of many.² We describe three patients who were diagnosed and treated for systemic lupus erythematosus (SLE), but investigations years after the original presentation and diagnosis led to the correct diagnosis of gluten sensitivity and treatment with a gluten-free diet.

CASE REPORTS

Case 1

A 20 month old girl presented with poor weight gain, intermittent malaise, and sweating. She was a normal delivery at term. She had chicken pox at the age of 4 months, which coincided with the onset of her symptoms. Weight gain was poor, but motor development was normal. She was intermittently sleepy and irritable, with tantrums and breath holding attacks. On examination she was pale and irritable, with mild flexural eczema. She was on the third centile for height and weight. Abnormal results included a raised erythrocyte sedimentation rate (ESR) of 70 mm/1st h, weakly positive antinuclear antibodies (ANA), IgA deficiency, positive smooth muscle antibodies, and raised anticardiolipin antibodies. Urine analysis and complement levels were normal. Her parents reported a facial rash, attributed to sun exposure.

On the basis of the available evidence a diagnosis of SLE was made, and treatment was started with steroids. There was some improvement in her overall clinical state, but the ESR continued to fluctuate. At the age of 4 she was noted to have poor enamel on her teeth and required teeth extractions. At the age of 6 she developed steroid related side effects and azathioprine was started. While receiving steroids and

azathioprine, ANA, double stranded DNA (dsDNA), and extractable nuclear antibodies (ENA) were negative.

At the age of 17 she was referred to an adult SLE clinic. On examination she had a psoriatic palmar skin rash but nothing else of note. Immunological testing disclosed negative ANA and ENA, dsDNA of 92 IU/ml (0–60), ESR of 29 mm/1st h, IgA deficiency, and normal C reactive protein (CRP). The possibility of gluten sensitivity was considered on the basis of the history and immunological profile. She tested positive for IgG anti gliadin antibodies, and a subsequent duodenal biopsy confirmed gluten sensitive enteropathy. A gluten-free diet was started, azathioprine was stopped, and the steroids withdrawn. Six months after the introduction of the diet she was asymptomatic and receiving no drugs. Her ESR was normal and the skin rash had resolved.

Case 2

A 53 year old woman developed blurred vision, headache, and generalised weakness at the age of 20. She improved spontaneously within several weeks. A year later she presented with identical symptoms and was treated with a course of adrenocorticotropic hormone. Three years later she was admitted with a history of recurrent severe headaches, heaviness of her legs, and asthenia. Investigations disclosed a normal computed tomography (CT) brain scan, visual evoked responses, and cerebrospinal fluid examination, a slight increase of anticardiolipin antibodies, raised rheumatoid factor, and dsDNA, but no ANA. An iron deficiency anaemia was attributed to menorrhagia. A brain magnetic resonance imaging (MRI) scan showed extensive white matter abnormalities not typical of multiple sclerosis. In view of the immunological picture and the presence of circulating anticardiolipin antibodies a diagnosis of SLE associated with antiphospholipid syndrome was made. She was given aspirin but remained symptomatic with episodic headaches and asthenia.

A few years later she complained of generalised arthralgia. There was no evidence of active synovitis. She was treated with steroids and methotrexate. She continued to complain of fatigue and headaches, which tended to be unilateral and very severe. Examination showed a left sided cataract with a divergent squint, mild left hemiparesis, and gait ataxia. Repeat MRI showed extensive white matter abnormalities with mild generalised atrophy. An immunological profile showed IgA deficiency, raised dsDNA antibodies, a minimal rise in anticardiolipin IgG antibodies, no ANA or ENA, and normal inflammatory markers (ESR and CRP). She had circulating IgG anti gliadin antibodies and the HLA typing

Abbreviations: ANA, antinuclear antibodies; ANF, antinuclear factor; CD, coeliac disease; CRP, C reactive protein; CT, computed tomography; dsDNA, double stranded DNA; ENA, extractable nuclear antibodies; ESR, erythrocyte sedimentation rate; MRI, magnetic resonance imaging; SLE, systemic lupus erythematosus

DQ2, which is seen in 90% of patients with gluten sensitive enteropathy. A subsequent duodenal biopsy was normal.

She was diagnosed as having gluten sensitivity with neurological manifestations (gluten ataxia, headache, and white matter abnormalities on MRI).³ She was advised to start a strict gluten-free diet. Six months after the introduction of a gluten-free diet her headaches subsided and the methotrexate was stopped.

Case 3

A 54 year old woman originally presented at the age of 40 with persistent headaches. She was found to have a raised ESR (60 mm/1st h) and mild neutropenia. Temporal artery biopsy was normal as was a CT head scan. Two years later she was referred because of epigastric pain. Gastroscopy and abdominal ultrasound were normal. She had a raised ESR, high globulins, negative antinuclear factor (ANF), and abnormal liver transaminases. An abdominal CT scan was normal.

Nine years after the initial presentation she complained of pruritus and intermittent facial oedema. She was diagnosed as having urticaria. There was no history of arthralgia, photosensitivity, or previous thrombotic episodes. She had an ESR of 76 mm/1st h, raised dsDNA at 301 IU/ml (normal range 0–60 IU/ml) but negative ANF, positive rheumatoid factor, normal complement levels, neutropenia of 0.9 (range $1.6\text{--}6.5 \times 10^9/l$) but no lymphopenia, raised anticardiolipin antibodies, and a negative Schirmer test. Her CRP was normal. Her main complaints were a headache and abdominal discomfort. A diagnosis of SLE was made. She was treated with aspirin.

A year later she was reviewed by the gastroenterologists who performed a colonoscopy, which was normal. A detailed review 13 years after the original presentation suggested that the immunological picture (raised dsDNA but normal ANF, neutropenia, high ESR) in combination with the gastrointestinal symptoms and persistent headache might be suggestive of gluten sensitivity. Immunological tests showed that she was positive for IgG and IgA antigliadin antibodies and had the HLA typing DQ2. She refused duodenal biopsy but agreed to the introduction of a gluten-free diet. Her headaches and gastrointestinal symptoms have since subsided and her ESR is now normal.

DISCUSSION

Gluten sensitivity has been likened to “a many-headed hydra” because of its diverse manifestations.⁴ Although most physicians may be familiar with the classic presentation of gluten sensitivity as an enteropathy (CD), it is worth bearing in mind that the prevalence of CD in the “healthy” population in European countries^{5,6} and the USA is as high as 1%. Therefore, for every patient presenting to a gastroenterologist with the classical presentation of one or more of diarrhoea, abdominal discomfort, bloating, weight loss, steatorrhoea, and/or anaemia, there are eight patients without gastrointestinal symptoms (silent CD).⁷ Furthermore gluten sensitivity may solely present with neurological dysfunction (ataxia and peripheral neuropathy being the commonest).² Only a third of patients presenting with neurological dysfunction due to gluten sensitivity will have evidence of an enteropathy on duodenal biopsy.⁸ The presence of an enteropathy is no longer a prerequisite for the diagnosis of gluten sensitivity. Small bowel mucosal lesions in patients with gluten sensitivity range from normal (grade 0) to irreversible hypoplastic (grade 4).¹ Patients with no enteropathy have antigliadin antibodies and HLA type in keeping with gluten sensitivity (for example, cases 2 and 3). A gluten-free diet appears to be effective in the treatment of these patients.⁹

IgA deficiency is 10 times commoner in patients with gluten sensitivity than in the healthy population.¹⁰ Given that all other gluten related antibodies are of the IgA class (endomysium and tissue transglutaminase), IgG antigliadin antibodies in this context are the only marker of gluten sensitivity. The high sensitivity of IgG antigliadin antibodies in relation to the whole spectrum of gluten sensitivity (with or without an enteropathy) is highlighted by those patients with no enteropathy but positive IgG antigliadin antibodies, who have the same genetic susceptibility (DQ2) as those with CD.⁸ In view of almost 100% specificity antiendomysium antibodies will only be positive in the presence of an enteropathy. The common association with other autoimmune diseases, the raised inflammatory markers, and the symptoms suggestive of an immune diathesis which characterise gluten sensitivity often result in a clinical and immunological picture that may lead to an erroneous diagnosis, as illustrated by these three cases.

Patients with CD developing SLE and vice versa have been reported, highlighting a possible association.^{11,12} Another report has shown that up to 23% of patients with CD have raised anti-dsDNA.¹³ This reflects our own experience of patients presenting with neurological dysfunction due to gluten sensitivity, in whom an increase of anti-dsDNA antibodies was seen in up to 20% (unpublished observation). These patients have negative ANF.

The prevalence of antigliadin antibodies in patients with SLE has been reported to be 23%.¹⁴ None of these patients had an enteropathy on biopsy. The conclusion was that there is no association between CD and SLE, but an association between gluten sensitivity and SLE cannot be excluded. More likely, however, is the possibility of misdiagnosis of SLE in patients with gluten sensitivity. Although it is important to be aware of the possible clustering of autoimmune diseases in the same person, it is more important to consider gluten sensitivity in the differential diagnosis of clinical scenarios such as those described above. Screening for the whole spectrum of gluten sensitivity may be easily and cost effectively undertaken by measuring circulating antigliadin antibodies (IgG and IgA), with endomysium and tissue transglutaminase antibodies being used as a marker of the presence of an enteropathy. Failure to do so may not only deprive the patient of the correct diagnosis and treatment (gluten-free diet) but also result in the unnecessary use of long term immunosuppressive drugs, with their associated morbidity.

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